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AN 1993-172621 [21] WPIDS
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TI **Skin whitening** cosmetics - contg. para-hydroxy
cinnamic acid derivs. as main component.

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PA (KAOS) KAO CORP

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The cosmetics contain p-hydroxycinnamic acid derivs. of formula (I) as
the

effective component. In (I) at least one of R1 and R2 is lower alkyl and
other is H; R3 = H or lower alkyl.

USE - The material has excellent skin whitening effect. Stain,
freckles and suntan are removed by applying it to that part. No
irritation

to skin.

Dwg. 0/0

TI **Skin whitening** cosmetics - contg. para-hydroxy
cinnamic acid derivs. as main component.

CLIPPEDIMAGE= JP405105620A
PAT-NO: JP405105620A
DOCUMENT-IDENTIFIER: JP 05105620 A
TITLE: BEAUTIFYING COSMETIC COMPRISING
P-HYDROXYCINNAMIC ACID DERIVATIVE AS
ACTIVE INGREDIENT

PUBN-DATE: April 27, 1993

INVENTOR-INFORMATION:

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COUNTRY

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APPL-NO: JP03266405

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INT-CL_(IPC): A61K007/48; A61K007/00

ABSTRACT:

PURPOSE: To obtain a beautifying cosmetic having excellently improving effects on skin pigmentation, capable of treating and moderating pigmented skin to return to a normal color of skin by locally applying the cosmetic to stain, freckle and pigmentation part after suntan.

CONSTITUTION: The objective cosmetic contains 0.01-50wt.%, preferably 0.1-20wt.% p-hydroxycinnamic acid of the formula (at least one of R_1 and R_2 is lower alkyl and the rest is H; R_3 is H or lower alkyl) such as p-hydroxy- β -methylcinnamic acid ethyl ester as an active ingredient. A dose is preferably 1-20mg based on 1cm² skin surface in the case of cream or ointment state and 1-10mg in the case of liquid preparation. The compound, for example, is obtained by condensing p-hydroxybenzaldehyde with an alkylmalonic acid in the presence of a base such as pyridine or piperidine and optionally esterifying.

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TITLE: Skin whitening cosmetics - contg. para-hydroxy:cinnamic acid
derivs. as

main component

PATENT-ASSIGNEE: KAO CORP[KAOS]

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BASIC-ABSTRACT: The cosmetics contain p-hydroxycinnamic acid derivs.
of formula

(I) as the effective component. In (I) at least one of R1 and R2 is lower
alkyl and other is H; R3 = H or lower alkyl.

USE - The material has excellent skin whitening effect. Stain, freckles and
suntan are removed by applying it to that part. No irritation to skin.

CHOSEN-DRAWING: Dwg.0/0

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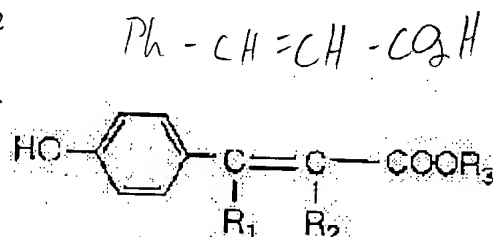
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(54) BEAUTIFYING COSMETIC COMPRISING P-HYDROXYCINNAMIC ACID DERIVATIVE AS ACTIVE INGREDIENT

(57)Abstract:

PURPOSE: To obtain a beautifying cosmetic having excellently improving effects on skin pigmentation, capable of treating and moderating pigmented skin to return to a normal color of skin by locally applying the cosmetic to stain, freckle and pigmentation part after suntan.

CONSTITUTION: The objective cosmetic contains 0.01-50wt.%, preferably 0.1-20wt.% p-hydroxycinnamic acid of the formula (at least one of R1 and R2 is lower alkyl and the rest is H; R3 is H or lower alkyl) such as p-hydroxy- β -methylcinnamic acid ethyl ester as an active ingredient. A dose is preferably 1-20mg based on 1cm² skin surface in the case of cream of ointment state and 1-10mg in the case of liquid preparation. The compound, for example, is obtained by condensing p-hydroxybenzaldehyde with an alkylmalonic acid in the presence of a base such as pyridine or piperidine and optionally esterifying.



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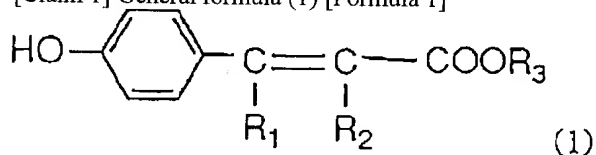
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CLAIMS

[Claim(s)]

[Claim 1] General formula (1) [Formula 1]



They are the whitening cosmetics which make an active principle the p-hydroxy cinnamic acid derivative expressed with (in at least the inside of a formula, and one side of R1 and R2 a low-grade alkyl group and the remainder show a hydrogen atom, and R3 shows a hydrogen atom or a low-grade alkyl group).

[Translation done.]

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DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Field of the Invention] It is safe and this invention relates to the whitening cosmetics excellent in the pigmentation improvement effect which make a p-hydroxy cinnamic acid derivative an active principle.

[0002]

[Description of the Prior Art] Follow the pigmentation after a stain, a freckle, and suntan on an aging, it seldom occurs, increases or comes to disappear, and serves as the trouble to the middle-aged and the elderly's skin. Although it is not [the sideration device of these hemochromatosis] yet clear, it is considered because the melanin synthesis function in an epidermis melanocyte rose by the solar beam of light especially ultraviolet rays, and operation of melanocyte tropic hormones etc. Moreover, cornification retardation-ization accompanied by the aging of a keratinocyte (keratinocyte) also delays the passage speed to the outside of epidermis, and is considered to discover the increase in the melanin-granule density in epidermis, i.e., the symptom which a pigmentation increases clinically, together with sthenia of melanin synthesis ability. Furthermore, those pigmentation sections exist locally and it is also considered the result which made the device in which local melanin synthesis sthenia of a melanocyte or melanin synthesis of a melanocyte was controlled modulate from differentiation arising clearly with surrounding normal skin color.

[0003] These acquired coloring matter, i.e., the medicine which makes even normal skin color recover the self-possessed section of melanin, is desired strongly, and many medicines were developed until now and it has been commercialized. For example, although the charge of makeup using the vitamin-C (L ascorbic acid) derivative which has the outstanding reduction ability in recent years had also been used, while difficulty was in the stability, the present condition was that an effect hardly accepts in external application.

[0004] On the other hand, although used as a medicine, like hydroquinone makes the treatment and the Negro skin of a stain white in the West, there is a problem in blending as a medicine from points, like there are this and a case where a problem is in the safety (stimulative, allergy nature) of the matter [itself], and a facula is produced. In addition, although various melanin inhibitors are reported, as a cinnamic acid derivative, p-hydroxy cinnamic acid (Brun, J.Soc.Cosmet.Chem., 25, and 61 (1974)) and the p-hydroxy cinnamic acid amide derivative (JP,62-56459,A) are known. However, the present condition is that the matter with which it is satisfied of both of safety to the pigmentation improvement effect and the skin enough is not known.

[0005]

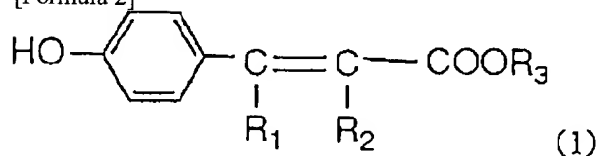
[Problem(s) to be Solved by the Invention] It is safe and this invention aims at offering the whitening cosmetics excellent in the pigmentation improvement effect.

[0006]

[Means for Solving the Problem] As a result of inquiring zealously that this invention persons should get the matter which it lets matter] a research of a melanin generation device pass, and decreases or vanishes a pigmentation, a specific p-hydroxy cinnamic acid derivative has melanin generation depressant action, found out that a manifestation of stimulative and allergy to the skin etc. moreover did not accept, and completed this invention.

[0007] That is, this invention is general formula (1) [0008] of a degree.

[Formula 2]



[0009] The whitening cosmetics which make an active principle the p-hydroxy cinnamic acid derivative expressed with (in at least the inside of a formula and one side of R1 and R2 a low-grade alkyl group and the remainder show a hydrogen atom, and R3 shows a hydrogen atom or a low-grade alkyl group) are offered.

[0010] As a p-hydroxy cinnamic acid derivative (1) used in this invention, p-*****-alpha-methyl cinnamic acid or its ester, p-*****-beta-methyl cinnamic acid, or its ester is mentioned as a desirable thing, for example. As a suitable compound, p-*****-beta-methyl ethyl-cinnamate ester can be mentioned especially.

[0011] A p-hydroxy cinnamic acid derivative (1) is compoundable according to it according to technique given in reference. A

p-hydroxy benzaldehyde, an alkyl malonic acid, etc. For example, a pyridine, How (Berman, J. Am. Chem. Soc., 80, and 4949 (1958)) to make it condense under presence of bases, such as a piperidine, and to esterify further if needed, A hydroxyl-group protector, dialkyl phosphono acetic ester, etc. of a p-hydroxy acetophenone system compound are made to condense under presence of bases, such as a sodium hydride. furthermore, it can obtain easily by the technique (Emmons, Org. Syn., V, and 547 (1973)) of carrying out a deprotection by the technique of hydrolysis and (or) common use if needed etc.

[0012] It is independent, or the above-mentioned p-hydroxy cinnamic acid derivative (1) can be blended with the whitening cosmetics of this invention combining two or more sorts, and especially the loadings have 0.1 - 20 desirable % of the weight 0.01 to 50% of the weight in a constituent.

[0013] Although the whitening cosmetics of this invention can be made into various gestalt, generally it is desirable to consider as the charges of makeup, such as the shape of the shape of the shape of the shape of the shape of a lotion and a milky lotion and a cream and salve and a stick, the shape of a solution by the organic solvent, the letter of a pack, and gel.

[0014] Arbitrary components other than a p-hydroxy cinnamic acid derivative (1) can be blended with the whitening cosmetics of this invention in the domain which does not spoil the effect of this invention, and the component usually blended with the charge of makeup, for example, a purified water, ethanol, an oily matter, a **** agent, a thickener, antiseptics, an emulsifier, a **** component, fine particles, perfume, emulsion stabilizer, pH regulator, etc. can be blended with them according to the pharmaceutical form. As an oily component, specifically A liquid paraffin, vaseline, a paraffine wax, Squalane, yellow bees wax, a carnauba wax, olive oil, lanolin, higher alcohol, The synthetic ester oil of a fatty acid, and higher alcohol and a fatty acid, silicon oil, etc. are mentioned. As a **** agent, a sorbitol, a xylitol, a glycerol, a maltitol, A propylene glycol, 1, 3-butylene glycol, 1, 4-butylene glycol, Pyrrolidone carboxylic-acid sodium, a lactic acid, a sodium lactate, polyoxypropylene fatty acid ester, A polyethylene glycol etc. is mentioned. as a thickener A carboxyvinyl polymer, A carboxymethyl cellulose, polyvinyl alcohol, a carrageenan, Electrolytes, such as water soluble polymers, such as gelatin, a sodium chloride, and potassium chloride, etc. are mentioned. As antiseptics, a urea, the methylparaben, an ethylparaben, a propylparaben, The butylparaben, a sodium benzoate, etc. are mentioned. as an emulsifier Polyoxyethylene alkyl ether, Polyoxyethylene fatty acid ester, polyoxyethylene sorbitan fatty acid ester, A glycerine fatty acid ester, polyglyceryl fatty acid ester, polyoxyethylene glycerine fatty acid ester, Nonionic surface active agents, such as polyoxyethylene hydrogenated castor oil and polyoxyethylene sorbitol fatty acid ester, are mentioned. As fine particles, talc, a sericite, a mica, a kaolin, a silica, a bentonite, A vermiculite, a zinc white, a mica, mica titanium, titanium oxide, a magnesium oxide, a zirconium oxide, a barium sulfate, red ocher, an iron oxide, ultramarine blue, etc. are mentioned, and buffers, such as a lactic-acid-sodium lactate and a citric-acid-sodium citrate, are mentioned as a pH regulator. Moreover, as various active principles, enhancement in a melanin depressor effect can be aimed at by adding an allantoin, vitamin-E acetate, glycyrrhizin, a coix seed, various vegetable extracts, etc. Furthermore, it can also consider as the charge of makeup which had the prevention effect and curative effect of suntan by adding various ultraviolet-absorption matter.

[0015] By applying to the affected parts, such as the inflammation of the skin by ultraviolet rays, a stain, a freckle, and the pigmentation section after suntan, locally, the whitening cosmetics of this invention can treat and improve this site, and can return it to normal skin color. Moreover, generally in the case of the tablet of the shape of the shape for example, of a cream, or salve, it is [1cm of skin sides] desirable [the dosage] in the case of 1-20mg per two, and a liquefied tablet to be referred to as 1-10mg similarly.

[0016]

[Example] Next, the example of reference, an example, and the example of an examination are given, and this invention is explained.

[0017] Heating churning of the mixture (synthetic :4-hydroxy benzaldehyde 2.44g [of example of reference 1p-*****-alpha-methyl cinnamic acid and its ethyl ester] (20mmol), 4.72g [of methylmalonic acids] (40mmol), and pyridine 25ml and piperidine 3.41g (40mmol)) was carried out for two days. This was poured into the mixture of 50ml of concentrated hydrochloric acids, and 100g of iced water after cooling, and the water layer was extracted twice by ether 200ml. Subsequently, the sodium-hydrogencarbonate aqueous solution was added 5%, and the organic layer was separated. The separated crystal was ****ed, after having added the diluted hydrochloric acid to this and making it acid. 584mg (3.28mmol) of p-*****-alpha-methyl cinnamic acid was obtained as white needlelike ** of 205.2-207.4 degrees C of the melting points. ¹H-NMR 12.2 (1H, brs) (CD₃SO₂d₆, TMS, delta), 9.79 (1H, s), 7.51 (1H, s), and 7.34 (2H, d, J= 8.4Hz), The heating reflux of 6.82 (2H, d, J= 8.4Hz), 300mg (1.68mmol) of 2.02(3H, s) p-*****-alpha-methyl cinnamic acid, two drops of hydrochloric acids, and the ethanol 10ml mixture was carried out for 16 hours. After distilling off a solvent by the evaporator, the residue was covered over the column chromatography (SiO₂, a hexane / ethyl-acetate =4), and was refined, and p-*****-alpha-methyl ethyl-cinnamate ester 0.29g (1.41mmol) was obtained as white powder of 83.7-84.9 degrees C of the melting points. ¹H-NMR (CDCl₃, TMS, delta) 7.63 (1H, s), 7.33 (2H, d, J= 8.4Hz), 6.87 (2H, d, J= 8.4Hz), 5.56 (1H, s), 4.27 (2H, q, J= 7.1Hz), 2.12 (3H, s), and 1.35 (3H, t, J= 7.1Hz) [0018] Three drops of concentrated hydrochloric acids (under ice-cooling) were added to mixture (synthetic :4-hydroxy acetophenone 10g (73.4mmol) of example of reference 2p-*****-beta-methyl cinnamic acid, and its ester, dihydropyran 6.79g (80.7mmol), and ether 50ml) at 0 degree C, and, subsequently it agitated for two days at the room temperature. After a reaction end, sodium hydroxide The crystal which added and (pH9) separated 0.5g and 30ml of saturation sodium hydrogencarbonates was ****ed. The recrystallization of this was carried out from hexane-ethyl acetate, and 4-(tetrahydro-2-*****-) acetophenone 12.9g (58.7mmol) was obtained as white needlelike **. ¹H-NMR 7.93 (2H, d, J= 8.9Hz) (CDCl₃, TMS, delta), 7.09 (2H, d, J= 8.9Hz) and 5.52 (1H, t, J= 3.1Hz), 3.86 (1H, m), 3.65 (1H, m), and 2.56 (3H, s), Into 1.48g (37.0mmol) of 2.2-1.4(6H, m) 60% sodium hydrides, and tetrahydrofuran 15ml mixture,

8.14g (36.3mmol) of diethyl phosphono ethyl acetate was covered for 30 minutes at the room temperature (20 degrees C), and, in addition, subsequently, it agitated at the room temperature for 1 hour. Next, the 4-(tetrahydro-2-******) acetophenone 8g (36.3mmol) tetrahydrofuran (30ml) solution was covered for 30 minutes, and, in addition, subsequently, carried out heating churning at 50 more degrees C with the room temperature for 1 hour for 1 hour. The tetrahydrofuran was distilled off after the reaction end, water was added, and it extracted by diethylether. an organic layer -- a saturated ammonium chloride solution -- subsequently it dried with sulfuric-anhydride magnesium after washing with saturation brine After distilling off a solvent by the evaporator, the residue was covered over the column chromatography (SiO₂, a hexane / ethyl-acetate =5), and was refined, and 4-(tetrahydro-2-*****)-beta-methyl ethyl-cinnamate ester 3.27g (11.3mmol) was obtained as a white crystal. 1H-NMR7.44 (2H, d, J= 8.8Hz) (CDCl₃, TMS, delta), 7.04 (2H, d, J= 8.8Hz) and 6.10 (1H, s), 5.45 (1H, s), 4.20 (2H, q, J= 7.1Hz), 3.89 (1H, m), 3.63 (1H, m), and 2.55 (3H, s), 2.2- 1.4 (6H) and 1.31 (3H, t, J= 7.1Hz) -- subsequently -- 4-(tetrahydro-2-*****)-beta-methyl ethyl-cinnamate ester 1.0g (3.44mmol) -- The heating reflux of p-toluenesulfonic acid and 50mg (0.26mmol) of monohydrates, and the ethanol 15ml mixture was carried out for 1 hour. After cooling, after condensing a solvent by the evaporator, the crystal which added and separated 10ml of water was ****ed. This was applied to the column chromatography (SiO₂, a hexane / ethyl-acetate =5), and was refined, and p-*****)-beta-methyl ethyl-cinnamate ester 0.67g (3.25mmol) was obtained as a white crystal of 94.2-95.2 degrees C of the melting points. 1H-NMR7.40 (2H, d, J= 8.6Hz) (CDCl₃, TMS, delta), 6.85 (2H, d, J= 8.6Hz) and 6.11 (1H, s), 5.79 (1H, s), 4.22 (2H, q, J= 7.1Hz), 2.56 (3H, s) and 1.32 (3H, t, J= 7.1Hz) -- 0.6g (2.1mmol) of 4-(tetrahydro-2-*****)-beta-methyl cinnamic acid, 3ml of 1N sodium-hydroxide aqueous solutions, and ethanol 1ml mixture were heated again for 4 hours The solvent was distilled off by the evaporator after cooling to a room temperature, and the crystal which added and separated 5ml of 1N hydrochloric acids was ****ed. 0.48g (1.8mmol) of 4-(tetrahydro-2-*****)-beta-methyl cinnamic acid was obtained as a white crystal. 1H-NMR7.47 (2H, d, J= 8.8Hz) (CDCl₃, TMS, delta), 7.06 (2H, d, J= 8.8Hz), 6.15 (1H, s), 5.47 (1H, s), 3.89 (1H, m), 3.65 (1H, m), 2.59 (3H, s), and 2.2-1.4 (6H, m) -- subsequently The heating reflux of 350mg (1.33mmol) p-toluenesulfonic-acid [of 4-(tetrahydro-2-*****)-beta-methyl cinnamic acid] and 14.6mg [of monohydrates], and tetrahydrofuran 5ml and the mixture of 1ml of water was carried out for 2 hours. After cooling, after condensing a solvent by the evaporator, the crystal which added and separated water was ****ed. When the recrystallization of this was carried out from hexane-ethyl acetate, 128mg (0.72mmol) of p-*****)-beta-methyl cinnamic acid was obtained as white needlelike ** of 140.3-141.0 degrees C of the melting points. 1H-NMR (CD₃ OD, TMS, delta)7.50 (2H, d, J= 8.6Hz), 6.88 (2H, d, J= 8.6Hz), 6.17 (1H, s), and 2.60 (3H, s) [0019] Example 1 Charge of face toilet type makeup : (composition) p-*****)-beta-methyl ethyl-cinnamate ester 5.0 (weight %) A glycerol 4.0 Polyoxyethylene hydrogenated castor oil 1.5 Ethanol 10.0 Pyrrolidone carboxylic-acid sodium 2.0 Perfume Minute amount Purified water Residue Sum 100.0 [0020] Example 2 Charge of oil essence type makeup : (composition) p-*****)-beta-methyl ethyl-cinnamate ester 5.0 (weight %) Mink oil 55.0 Wheat germ oil 40.0 Sum 100.0 [0021] Example 3 W/charge of O type moisture cream type makeup: (composition) p-*****)-beta-methyl cinnamic acid 5.0 (weight %) Vaseline 6.0 Cholesterol 0.6 Cetanol 0.5 Sorbitansesquiolate 2.0 Liquefied lanolin 4.0 Isopropyl palmitate 8.0 Squalene 10.0 Solid paraffin 4.0 Butylparaben 0.1 Methylparaben 0.1 Glycerol 3.0 Perfume 0.2 Purified water Residue Sum 100.0 [0022] Example 4 O/charge of W type moisture cream type makeup: (composition) p-*****)-alpha-methyl ethyl-cinnamate ester 5.0 (weight %) Stearin acid 2.0 Cetanol 4.0 Vaseline 5.0 Squalene 8.0 Hardening palm oil 4.0 Polyoxyethylenesorbitan monostearate (20E.O.) 1.4 Lipophilic type glyceryl monostearate 2.4 Butylparaben 0.1 Methylparaben 0.1 glycerols 3.0 Dipropylene glycol 3.0 The L-arginine 10.0 (%) potassium hydroxide 0.2 Perfume 0.2 Purified water Residue Sum 100.0 [0023] Example 5 Charge of milky lotion type makeup: (composition) p-*****)-alpha-methyl ethyl-cinnamate ester 5.0 (weight %) Stearin acid 1.0 Cetanol 2.0 Vaseline 2.5 Squalene 4.0 Hardening palm oil 2.0 Polyoxyethylenesorbitan monostearate (20E.O.) 1.4 Lipophilic type glyceryl monostearate 1.2 Butylparaben 0.1 Methylparaben 0.1 glycerols 3.0 Dipropylene glycol 3.0 Potassium hydroxide 0.2 Carboxyvinyl polymer 0.2 Perfume 0.2 Purified water Residue Sum 100.0 [0024] Example 6 Charge of packed type (paste-like peeled off type) makeup: (composition) p-*****)-alpha-methyl cinnamic acid 10.0 (weight %) Polyvinyl alcohol 12.0 Carboxymethylcellulose sodium 3.0 Dipropylene glycol 2.0 Glycerol 2.0 Ethanol 5.0 Olive oil 3.0 Polyoxyethylene hydrogenated castor oil (30E.O.) 0.5 Titanium oxide 8.0 Kaolin 6.0 Perfume 0.1 Methylparaben 0.1 Purified water Residue Sum 100.0 [0025] Example 7 Charge of salve type makeup: (composition) p-*****)-beta-methyl ethyl-cinnamate ester 10.0 (weight %) White vaseline 90.0 Sum 100.0 [0026] Example 8 Charge of solution type makeup: (composition) p-*****)-beta-methyl ethyl-cinnamate ester 5.0 (weight %) Ethanol 95.0 Sum 100.0 [0027] The regions-of-back hair follicle of the C57BL system mouse on eight - after-the-birth the 11th which is performing briskly the evaluation test-method:melanin synthesis by the tyrosinase activity of an example of examination 1 mouse regions-of-back skin hair-follicle organ-culture system was cultivated for three - four days. It added so that an evaluation sample might be set to last concentration 5mM to the culture medium under incubation, and the enzyme and tyrosinase activity

which bears melanin synthesis were measured with the amount (3HOH) of disengagement tritiums from a 3 and 5-3H-thyrosin, and it evaluated as compared with control. This result is shown in Table 1.

He has no depressor effect. 00 - 5% **5 - 35% +35%- ++ result : [0028]

[Table 1]

	抑制効果
p-ヒドロキシ- α -メチル桂皮酸エチルエステル	+
p-ヒドロキシ- β -メチル桂皮酸エチルエステル	++
p-ヒドロキシ- α -メチル桂皮酸	±
p-ヒドロキシ- β -メチル桂皮酸	±
p-ヒドロキシ桂皮酸 (比較例)	0

[0029] the example 2 of an examination -- the fading improvement effect over a pigmentation was investigated after forming a pigmentation, using the brown guinea pig which has acquired melanin maculation ability as a laboratory animal

Test-method: Using the brown guinea pig (guinea pig which skin color is similar with yellow-skinned races' thing, and coloring matter spots will begin to produce like human being in abbreviation four days after irradiation of ultraviolet rays, and will carry out a melanism most in about eight days), regions-of-back hair of this guinea pig was *****ed by hair clipper, and it *****ed with the electric shaver further. UVA (BLB lamp, 3.1mW/cm²) was irradiated for 5 minutes after injecting 8-methoxy psoralen (PUVA) intraperitoneally to this guinea pig. From the 15 days back of irradiation, produced PUVA coloring matter maculation site was followed between a total of 1 30 days twice per day, and 5% solution (ethanol 80%, 20% of water) of an evaluation sample (p-*****-beta-methyl ethyl-cinnamate ester) was applied to it. The macro-scopic judging of the photographic density of skin color was carried out in the criterion shown below, it averaged the evaluating point, and measured the effect. This result is shown in Table 2.

Criterion 0: Don't accept a pigmentation.

1: Don't twist indistinctly [boundary] but accept a kana pigmentation.

2: a boundary -- accept the pigmentation of a degree clear middle

3: a boundary -- accept the pigmentation of a clear intensity

Result : [0030]

[Table 2]

	塗布前	30日後
p-ヒドロキシ- β -メチル桂皮酸エチルエステル	2.5	1.6
対照 (エタノールのみを塗布)	2.6	2.3

[0031]

[Effect of the Invention] The whitening cosmetics of this invention are excellent in the pigmentation improvement effect, differ in the conventional sun block which prevents suntan beforehand, by applying to the stain of the skin, a freckle, and the pigmentation section after suntan locally, can treat and improve this site and can return it to normal skin color. Moreover, a manifestation of stimulative and allergy etc. does not accept, but the whitening cosmetics of safety of this invention are high. [as opposed to the skin in the p-hydroxy cinnamic acid derivative (1) which is an active principle]

[Translation done.]

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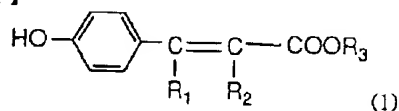
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(54)【発明の名称】 p-ヒドロキシ桂皮酸誘導体を有効成分とする美白化粧品

(57)【要約】

【構成】 一般式(1)

【化1】



(式中、R₁とR₂の少なくとも一方は低級アルキル基、残りは水素原子を、R₃は水素原子または低級アルキル基を示す)で表わされるp-ヒドロキシ桂皮酸誘導体を有効成分とする美白化粧品。

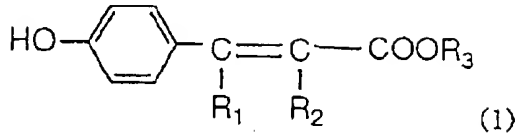
【効果】 本発明の美白化粧品は、色素沈着改善効果に優れ、皮膚のしみ、そばかす、日焼け後の色素沈着部に局所的に適用することにより、該部位を治療・改善し、正常な皮膚色に戻すことができる。また皮膚に対する刺激性、アレルギーの発現等も認められず、安全性の高いものである。

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【特許請求の範囲】

【請求項1】 一般式(1)

【化1】



(式中、 R_1 と R_2 の少なくとも一方は低級アルキル基、残りは水素原子を、 R_3 は水素原子または低級アルキル基を示す)で表わされるp-ヒドロキシ桂皮酸誘導体を有効成分とする美白化粧品。

【発明の詳細な説明】

【0001】

【産業上の利用分野】本発明は、p-ヒドロキシ桂皮酸誘導体を有効成分とする、安全でかつ色素沈着改善効果に優れた美白化粧品に関する。

【0002】

【従来の技術】しみ、そばかすおよび日焼け後の色素沈着は、加齢に伴い発生、増加あるいは消失しにくくなり、中高年齢層の肌の悩みとなっている。これらの色素沈着症の発症機構は、未だ明確にはされていないが、太陽光線、特に紫外線や、メラノサイト刺激ホルモン等の作用により、表皮メラノサイトでのメラニン合成機能が亢進したためと考えられる。また、表皮角化細胞(ケラチノサイト)の加齢に伴う角化遅延化も、表皮外への排泄速度を遅延させ、メラニン合成能の亢進と合わせて、表皮内のメラニン顆粒密度の増加、即ち臨床的に色素沈着が増加する症状を発現するものと考えられる。更にこれらの色素沈着部は局部的に存在し、周囲の正常皮膚色と明らかに差異が生ずることより、メラノサイトの局所的なメラニン合成亢進、あるいはメラノサイトのメラニン合成をコントロールする機構を変調せしめた結果とも考えられる。

【0003】これらの後天的な色素、即ちメラニンの沈着部を正常な皮膚色にまで回復させる薬剤が強く望まれており、これまでも多くの薬剤が開発され商品化されてきた。例えば、近年、優れた還元能を有するビタミンC(L-アスコルビン酸)誘導体を用いた化粧品も用いられてきたが、安定性に難があるとともに、外用では効果がほとんど認められないのが現状であった。

【0004】一方、欧米において、ハイドロキノンがしみの治療や黒人皮膚を白くする等の薬剤として用いられているが、これも物質自体の安全性(刺激性、アレルギー性)に問題があり、また白斑を生じさせるケースもあるなどの点から薬剤として配合することには問題がある。その他にも種々のメラニン抑制剤が報告されているが、桂皮酸誘導体としては、p-ヒドロキシ桂皮酸(Brun, J. Soc. Cosmet. Chem., 25, 61(1974))やp-ヒドロキシ桂皮酸アミド誘導体(特開昭62-56459号公報)が知

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られている。しかしながら、色素沈着改善効果及び皮膚に対する安全性の両者を充分満足する物質は知られていないのが現状である。

【0005】

【発明が解決しようとする課題】本発明は、安全でかつ色素沈着改善効果に優れた美白化粧品を提供することを目的とする。

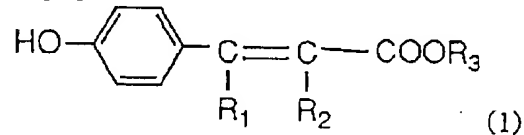
【0006】

【課題を解決するための手段】本発明者らは、メラニン生成機構の研究を通して色素沈着を減少あるいは消失させる物質を得るべく鋭意検討した結果、特定のp-ヒドロキシ桂皮酸誘導体はメラニン生成抑制作用を有し、しかも皮膚に対する刺激性、アレルギーの発現等が認められないことを見出し、本発明を完成した。

【0007】すなわち、本発明は次の一般式(1)

【0008】

【化2】



【0009】(式中、 R_1 と R_2 の少なくとも一方は低級アルキル基、残りは水素原子を、 R_3 は水素原子または低級アルキル基を示す)で表わされるp-ヒドロキシ桂皮酸誘導体を有効成分とする美白化粧品を提供するものである。

【0010】本発明において用いられるp-ヒドロキシ桂皮酸誘導体(1)としては、例えば、p-ヒドロキシ- α -メチル桂皮酸またはそのエステル、p-ヒドロキシ- β -メチル桂皮酸またはそのエステルなどが好ましいものとして挙げられる。特に好適な化合物としては、p-ヒドロキシ- β -メチル桂皮酸エチルエステルを挙げることができる。

【0011】p-ヒドロキシ桂皮酸誘導体(1)は、文献記載の方法に従って、あるいはそれに準じて合成でき、例えば、p-ヒドロキシベンズアルデヒドとアルキルマロン酸等をピリジン、ピペリジン等の塩基の存在下で縮合させ、更に必要に応じてエステル化する方法(Berman, J. Am. Chem. Soc., 80, 4949(1958))、p-ヒドロキシアセトフェノン系化合物の水酸基保護体とジアルキルホスホ酢酸エステル等を水素化ナトリウム等の塩基の存在下で縮合させ、更に必要に応じて加水分解および(または)慣用の方法で脱保護する方法(Emmons, Org. Syn., V, 547(1973))等によって容易に得ることができる。

【0012】本発明の美白化粧品には、上記p-ヒドロキシ桂皮酸誘導体(1)を、単独で、または二種以上を組み合わせて配合することができ、その配合量は、組成物中に0.01~50重量%、特に0.1~20重量%が好ましい。

【0013】本発明の美白化粧品は、種々の形態にする

ことができるが、一般には、ローション状、乳液状、クリーム状、軟膏状、スティック状、有機溶媒による溶液状、パック状、ゲル状等の化粧料とするのが好ましい。

【0014】本発明の美白化粧料には、本発明の効果を損ねない範囲でp-ヒドロキシ桂皮酸誘導体(1)以外の任意の成分を配合することができ、その剤型に応じて、化粧料に通常配合される成分、例えば精製水、エタノール、油性物質、保湿剤、増粘剤、防腐剤、乳化剤、薬効成分、粉体、香料、乳化安定剤、pH調整剤等を配合することができる。具体的には、油性成分としては流動パラフィン、ワセリン、パラフィンワックス、スクワラン、ミツロウ、カルナウバロウ、オリーブ油、ラノリン、高級アルコール、脂肪酸、高級アルコールと脂肪酸の合成エステル油、シリコン油等が挙げられ、保湿剤としてはソルビトール、キシリトール、グリセリン、マルチトール、プロピレングリコール、1,3-ブチレングリコール、1,4-ブチレングリコール、ピロリドンカルボン酸ナトリウム、乳酸、乳酸ナトリウム、ポリオキシプロピレン脂肪酸エステル、ポリエチレングリコール等が挙げられ、増粘剤としてはカルボキシビニルポリマー、カルボキシメチルセルロース、ポリビニルアルコール、カラギーナン、ゼラチン等の水溶性高分子、塩化ナトリウム、塩化カリウム等の電解質などが挙げられ、防腐剤としては尿素、メチルパラベン、エチルパラベン、プロピルパラベン、ブチルパラベン、安息香酸ナトリウム等が挙げられ、乳化剤としてはポリオキシエチレンアルキルエーテル、ポリオキシエチレン脂肪酸エステル、ポリオキシエチレンソルビタン脂肪酸エステル、グリセリン脂肪酸エステル、ポリグリセリン脂肪酸エステル、ポリオキシエチレングリセリン脂肪酸エステル、ポリオキシエチレン硬化ヒマシ油、ポリオキシエチレンソルビトール脂肪酸エステル等の非イオン界面活性剤が挙げられ、粉体としてはタルク、セリサイト、マイカ、カオリン、シリカ、ベントナイト、バーミキュライト、亜鉛華、雲母、雲母チタン、酸化チタン、酸化マグネシウム、酸化ジルコニウム、硫酸バリウム、ベンガラ、酸化鉄、群青等が挙げられ、pH調整剤としては乳酸-乳酸ナトリウム、クエン酸-クエン酸ナトリウム等の緩衝剤が挙げられる。また種々の有効成分として、アラントイン、ビタミンEアセテート、グリチルリチン、ヨクイニン、各種植物抽出物等を添加することにより、メラニン抑制効果の向上を図ることができる。更に、種々の紫外線吸収物質を添加することにより、日焼けの予防効果と治療効果を兼ね備えた化粧料とすることもできる。

【0015】本発明の美白化粧料は、紫外線による皮膚の炎症、しみ、そばかす、日焼け後の色素沈着部等の患部に局所的に適用することにより、該部位を治療・改善し、正常な皮膚色に戻すことができる。また、一般にその用量は、例えばクリーム状又は軟膏状の製剤の場合、皮膚面1cm²当り1~20mg、液状製剤の場合、同じく1

~10mgとするのが好ましい。

【0016】

【実施例】次に、参考例、実施例および試験例を挙げて本発明を説明する。

【0017】参考例1

p-ヒドロキシ- α -メチル桂皮酸およびそのエチルエステルの合成：4-ヒドロキシベンズアルデヒド2.44g (20mmol)、メチルマロン酸4.72g (40mmol)、ヒリジン25mlおよびピペリジン3.41g (40mmol)の混合物を2日間加熱撹拌した。冷却後、これを濃塩酸50mlと氷水100gの混合物に注ぎ込み、水層をエーテル200mlで2回抽出した。次いで5%炭酸水素ナトリウム水溶液を加え有機層を分離した。これに希塩酸を加え酸性にした後、析出した結晶を濾取した。融点205.2~207.4℃の白色針状晶としてp-ヒドロキシ- α -メチル桂皮酸584mg (3.28mmol)を得た。

¹H-NMR(CDCl₃, TMS, δ)

12.2(1H, brs), 9.79(1H, s), 7.51(1H, s), 7.34(2H, d, J=8.4Hz), 6.82(2H, d, J=8.4Hz), 2.02(3H, s)

20 p-ヒドロキシ- α -メチル桂皮酸300mg (1.68mmol)、塩酸2滴およびエタノール10mlの混合物を16時間加熱還流した。溶媒をエバポレーターで留去したのち、残留物をカラムクロマトグラフィー(SiO₂, ヘキサン/酢酸エチル=4)にかけて精製し、融点83.7~84.9℃の白色粉末としてp-ヒドロキシ- α -メチル桂皮酸エチルエステル0.29g (1.41mmol)を得た。

¹H-NMR(CDCl₃, TMS, δ)

7.63(1H, s), 7.33(2H, d, J=8.4Hz), 6.87(2H, d, J=8.4Hz), 5.56(1H, s), 4.27(2H, q, J=7.1Hz), 2.12(3H, s), 1.35(3H, t, J=7.1Hz)

【0018】参考例2

p-ヒドロキシ- β -メチル桂皮酸およびそのエステルの合成：4-ヒドロキシアセトフェノン10g (73.4mmol)、ジヒドロピラン6.79g (80.7mmol)およびエーテル50mlの混合物に0℃で(氷冷下)濃塩酸3滴を加え、次いで室温で2日間撹拌した。反応終了後、水酸化ナトリウム0.5gおよび飽和炭酸水素ナトリウム30mlを加え(pH9)、析出した結晶を濾取した。これをヘキサン-酢酸エチルより再結晶化し、白色針状晶として4-(テトラヒドロ-2-ピラニロキシ)アセトフェノン12.9g (58.7mmol)を得た。

¹H-NMR(CDCl₃, TMS, δ)

7.93(2H, d, J=8.9Hz), 7.09(2H, d, J=8.9Hz), 5.52(1H, t, J=3.1Hz), 3.86(1H, m), 3.65(1H, m), 2.56(3H, s), 2.2-1.4(6H, m)

60%水素化ナトリウム1.48g (37.0mmol)、テトラヒドロフラン15mlの混合物に室温(20℃)でジエチルホスホ酢酸エチル8.14g (36.3mmol)を30分間かけて加え、次いで室温で1時間撹拌した。次に4-(テトラヒドロ-2-ピラニロキシ)アセトフェノン8g (36.3mmol)のテト

ラヒドロフラン (30ml) 溶液を30分間かけて加え、次いで室温で1時間、更に50℃で1時間加熱撹拌した。反応終了後、テトラヒドロフランを留去し、水を加え、ジエチルエーテルで抽出した。有機層を飽和塩化アンモニウム水溶液、次いで飽和食塩水で洗浄後、無水硫酸マグネシウムで乾燥した。溶媒をエバポレーターで留去したのち、残留物をカラムクロマトグラフィー (SiO₂, ヘキサン/酢酸エチル=5) にかけて精製し、白色結晶として4-(テトラヒドロ-2-ピラニロキシ)-β-メチル桂皮酸エチルエステル3.27g (11.3mmol) を得た。

¹H-NMR (CDCl₃, TMS, δ)

7.44(2H, d, J=8.8Hz), 7.04(2H, d, J=8.8Hz), 6.10(1H, s), 5.45(1H, s), 4.20(2H, q, J=7.1Hz), 3.89(1H, m), 3.63(1H, m), 2.55(3H, s), 2.2-1.4(6H), 1.31(3H, t, J=7.1Hz)

次いで4-(テトラヒドロ-2-ピラニロキシ)-β-メチル桂皮酸エチルエステル1.0g (3.44mmol)、p-トルエンスルホン酸・一水和物50mg (0.26mmol) およびエタノール15mlの混合物を1時間加熱還流した。冷却後、溶媒をエバポレーターで濃縮したのち、水10mlを加え析出した結晶を濾取した。これをカラムクロマトグラフィー (SiO₂, ヘキサン/酢酸エチル=5) にかけて精製し、融点94.2~95.2℃の白色結晶として、p-ヒドロキシ-β-メチル桂皮酸エチルエステル0.67g (3.25mmol) を得た。

¹H-NMR (CDCl₃, TMS, δ)

7.40(2H, d, J=8.6Hz), 6.85(2H, d, J=8.6Hz), 6.11(1H, *

化粧水型化粧料:

(組成)

p-ヒドロキシ-β-メチル桂皮酸エチルエステル	5.0 (重量%)
グリセリン	4.0
ポリオキシエチレン硬化ヒマシ油	1.5
エタノール	10.0
ピロリドンカルボン酸ナトリウム	2.0
香料	微量
精製水	残量
合計	100.0

【0020】実施例2

オイルエッセンス型化粧料:

(組成)

p-ヒドロキシ-β-メチル桂皮酸エチルエステル	5.0 (重量%)
ミンク油	55.0
小麦胚芽油	40.0
合計	100.0

【0021】実施例3

W/O型モイスタークリーム型化粧料:

(組成)

p-ヒドロキシ-β-メチル桂皮酸	5.0 (重量%)
ワセリン	6.0
コレステロール	0.6
セタノール	0.5

*s), 5.79(1H, s), 4.22(2H, q, J=7.1Hz), 2.56(3H, s), 1.32(3H, t, J=7.1Hz)

また、4-(テトラヒドロ-2-ピラニロキシ)-β-メチル桂皮酸0.6g (2.1mmol)、1N水酸化ナトリウム水溶液3mlおよびエタノール1mlの混合物を4時間加熱した。室温に冷却後、溶媒をエバポレーターで留去し、1N塩酸5mlを加え、析出した結晶を濾取した。白色結晶として4-(テトラヒドロ-2-ピラニロキシ)-β-メチル桂皮酸0.48g (1.8mmol) を得た。

¹H-NMR (CDCl₃, TMS, δ)

7.47(2H, d, J=8.8Hz), 7.06(2H, d, J=8.8Hz), 6.15(1H, s), 5.47(1H, s), 3.89(1H, m), 3.65(1H, m), 2.59(3H, s), 2.2-1.4(6H, m)

次いで、4-(テトラヒドロ-2-ピラニロキシ)-β-メチル桂皮酸350mg (1.33mmol) p-トルエンスルホン酸・一水和物14.6mg、テトラヒドロフラン5mlおよび水1mlの混合物を2時間加熱還流した。冷却後、溶媒をエバポレーターで濃縮したのち、水を加え、析出した結晶を濾取した。これをヘキサン-酢酸エチルより再結晶化すると融点140.3~141.0℃の白色針状晶としてp-ヒドロキシ-β-メチル桂皮酸128mg (0.72mmol) を得た。

¹H-NMR (CD₃OD, TMS, δ)

7.50(2H, d, J=8.6Hz), 6.88(2H, d, J=8.6Hz), 6.17(1H, s), 2.60(3H, s)

【0019】実施例1

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ソルビタンセスキオレート	2.0
液状ラノリン	4.0
イソプロピルパルミテート	8.0
スクワレン	10.0
固型パラフィン	4.0
ブチルパラベン	0.1
メチルパラベン	0.1
グリセリン	3.0
香料	0.2
精製水	残量
合計	100.0

【0022】実施例4

O/W型モイスタークリーム型化粧料：

(組成)

p-ヒドロキシ- α -メチル桂皮酸エチルエステル	5.0 (重量%)
ステアリン酸	2.0
セタノール	4.0
ワセリン	5.0
スクワレン	8.0
硬化パーム油	4.0
ポリオキシエチレンソルビタンモノステアレート(20E.O.)	1.4
親油型モノステアリン酸グリセリン	2.4
ブチルパラベン	0.1
メチルパラベン	0.1
グリセリン	3.0
ジプロピレングリコール	3.0
L-アルギニン10.0(%)水酸化カリウム	0.2
香料	0.2
精製水	残量
合計	100.0

【0023】実施例5

乳液型化粧料：

(組成)

p-ヒドロキシ- α -メチル桂皮酸エチルエステル	5.0 (重量%)
ステアリン酸	1.0
セタノール	2.0
ワセリン	2.5
スクワレン	4.0
硬化パーム油	2.0
ポリオキシエチレンソルビタンモノステアレート(20E.O.)	1.4
親油型モノステアリン酸グリセリン	1.2
ブチルパラベン	0.1
メチルパラベン	0.1
グリセリン	3.0
ジプロピレングリコール	3.0
水酸化カリウム	0.2
カルボキシビニルポリマー	0.2
香料	0.2
精製水	残量
合計	100.0

【0024】実施例6

パック型（ペースト状ピールオフタイプ）化粧品：

（組成）

p-ヒドロキシ- α -メチル桂皮酸	10.0 (重量%)
ポリビニルアルコール	12.0
カルボキシメチルセルロースナトリウム	3.0
ジプロピレングリコール	2.0
グリセリン	2.0
エタノール	5.0
オリーブ油	3.0
ポリオキシエチレン硬化ヒマシ油(30E.O.)	0.5
酸化チタン	8.0
カオリン	6.0
香料	0.1
メチルパラベン	0.1
精製水	残量
合計	100.0

【0025】実施例7

軟膏型化粧品：

（組成）

p-ヒドロキシ- β -メチル桂皮酸エチルエステル	10.0 (重量%)
白色ワセリン	90.0
合計	100.0

【0026】実施例8

液剤型化粧品：

（組成）

p-ヒドロキシ- β -メチル桂皮酸エチルエステル	5.0 (重量%)
エタノール	95.0
合計	100.0

【0027】試験例1

30* 果を表1に示す。

マウス背部皮膚毛包器官培養系のチロシナーゼ活性による評価

抑制効果

なし

0

試験方法：メラニン合成を盛んに行っている生後8～11

0～5%

±

日のC57BL系マウスの背部毛包を3～4日間培養した。

5～35%

+

培養中の培養液に評価サンプルを最終濃度5mMになるよ

35%～

++

うに添加し、メラニン合成を担う酵素・チロシナーゼ活

結果：

性を3,5-³H-チロシンからの遊離トリチウム量 (³HOH)

【0028】

により測定し、コントロールと比較し評価した。この結*

【表1】

	抑制効果
p-ヒドロキシ- α -メチル桂皮酸エチルエステル	+
p-ヒドロキシ- β -メチル桂皮酸エチルエステル	++
p-ヒドロキシ- α -メチル桂皮酸	±
p-ヒドロキシ- β -メチル桂皮酸	±
p-ヒドロキシ桂皮酸（比較例）	0

【0029】試験例2

※50※後天的なメラニン色素斑形成能を有する褐色モルモット

を実験動物として用い、色素沈着を形成後、色素沈着に対する退色改善効果を調べた。

試験方法：褐色モルモット（皮膚色が黄色人種のものと同様紫外線の照射後約4日で色素斑が生じ始め、約8日間に最も黒化するモルモット）を用い、該モルモットの背部毛をバリカンにて刈毛し、更に電気カミソリにて剃毛した。このモルモットに8-メトキシソラレン（PUVA）を腹腔内投与後、UVA（BLBランプ、3.1mW/cm²）を5分間照射した。照射15日後より、生じたPUVA色素斑形成部位に評価サンプル（p-ヒドロキシ-β-メチル桂皮酸エチルエステル）の5%溶液（エタノール80%、水20%）を1日2回計30日間連続して塗布した。皮*

* 膚色の黒化度は以下に示す判定規準にて肉眼判定し、評価点を平均しその効果を測定した。この結果を表2に示す。

判定規準

0：色素沈着を認めない。

1：境界不明瞭なわずかな色素沈着を認める。

2：境界明瞭な中程度の色素沈着を認める。

3：境界明瞭な強度の色素沈着を認める。

結果：

【0030】

【表2】

	塗布前	30日後
p-ヒドロキシ-β-メチル桂皮酸エチルエステル	2.5	1.6
対照（エタノールのみを塗布）	2.6	2.3

【0031】

【発明の効果】本発明の美白化粧品は、色素沈着改善効果に優れ、予め日焼けを防止する従来のサンスクリーン剤等とは異なり、皮膚のしみ、そばかす、日焼け後の色素沈着部に局所的に適用することにより、該部位を治療※

※・改善し、正常な皮膚色に戻すことができるものである。また、有効成分であるp-ヒドロキシ桂皮酸誘導体(1)は、皮膚に対する刺激性、アレルギーの発現等が認められず、本発明の美白化粧品は安全性の高いものである。